UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:

MIRENA IUS LEVONORGESTREL-RELATED PRODUCTS LIABILITY LITIGATION (NO. II)

17-MD-2767 (PAE)
17-MC-2767 (PAE)

This Document Relates To All Actions

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF OMNIBUS MOTION TO EXCLUDE GENERAL CAUSATION EXPERT TESTIMONY OF ROBERT LANGER, M.D., M.P.H.

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I. Introduction

Dr. Langer's opinions share all of the same problems as identified in the Omnibus Brief, plus several more: none of his math makes sense. Dr. Langer admits that he assumes preferential prescribing of Mirena to obese women is so significant (albeit impossible for him to quantify) that Mirena users will develop intracranial hypertension at a rate far higher than the rate at which obese women develop intracranial hypertension, a mathematical impossibility. When Dr. Langer "corrects" Valenzuela 2017, he produces "control" groups that have intracranial hypertension at rates far higher than any population ever studied. When he attempts to justify the estimates underlying those "control" groups, he mixes together disparate studies, making an essential part of his calculation the assumption that women who use contraception in one study do not use contraception in another contemporaneous study.

Although Dr. Langer provides opinions about adverse event disproportionality, Bayer withheld from Dr. Langer their own internal disproportionality analysis. When presented with the numbers, Dr. Langer agreed they were supportive of a causal association, the exact opposite of the conclusion in his paper.

Dr. Langer's opinions are unreliable and were produced by an unreliable method without reviewing the admittedly relevant data. His testimony should be excluded.

II. Standard of Review

Plaintiffs' incorporate by reference the Standard of Review in their Omnibus Motion to Exclude, § II.

As stated there, Plaintiffs submit the *Daubert* factors[1] are useful when assessing the

[1] That is, (1) whether the expert's technique or theory can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether there is a high error rate for the expert's technique, and whether there are standards controlling the technique's operation; and (4) whether the expert's technique or theory is generally accepted by the relevant scientific community. 509 U.S. at 592-94.

experts' *epidemiological* opinions, which are the only opinions that Dr. Langer is qualified to give. Epidemiological methods, such as applying Bradford Hill, reaching conclusions about the prevalence of obesity among Mirena users (or about the extent of Mirena use among a population), or calculating the effect of a potential confounding variable on a case-control study, all have some degree of "error rate" and "standards controlling the technique's operation." Dr. Langer created "2x2" tables to calculate odds ratios, which the Court can do itself using the same tool most of the experts used.[2] Dr. Langer also discusses selection of cases and controls in case-control studies, an issue for which there is literature designed to help "the uninitiated."[3]

Critically here, an expert's opinion is inadmissible if it "is connected to existing data only by the *ipse dixit* of the expert," for a "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Joiner*, 522 U.S. at 146; accord *Louis Vuitton*, 209 F.Supp.3d at 644. To be sure, "no one denies that an expert might draw a conclusion from a set of observations based on extensive and specialized experience," *Kumho Tire Co.* at 156, but the expert must still "employ[ ] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *id.* at 152. The Court's prior formulation, i.e., looking to whether the methodology and analysis can be "challenged in any objective sense," is a prudent and appropriate approach supported by the case law. To put it another way, when assessing whether an expert uses a reliable methodology to reach a particular conclusion, is it possible to follow the expert's steps, confirm their conclusion, and challenge the various steps along the way?

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[2] See http://openepi.com/TwobyTwo/TwobyTwo.htm

[3] See British Medical Journal, *Epidemiology for the uninitiated*, specifically Chapter 8: http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/8-case-control-and-cross-sectional

III. Dr. Langer Did Not Apply Any Reliable Methodology To Issues Relevant To General Causation

Dr. Langer recognizes Bradford Hill as "one useful methodology," *Report* p. 8, but Dr. Langer applies it in a threadbare fashion, apparently because he felt he was excused from applying it at all. Dr. Langer used his *ipse dixit* rejection of Valenzuela 2017 as an excuse for not rigorously applying Bradford Hill, p. 9, based upon his assertion that Bradford Hill cannot be used until an epidemiological study free from any conceivable limitations has shown a statistically significant increase in the risk. At deposition, he abandoned this argument, admitting Bradford Hill can be applied even where the association is "not necessarily statistically significant," where it was seen in "disproportionate adverse event reporting," or in "consistent reports in case series," or in "consistent reports in small population studies." *Deposition of Dr. Langer*, 172:6-174:1. There can be no doubt all of these criteria are met; Dr. Langer himself admitted the "disproportionate adverse event reporting" shown by Bayer's own database, which he was not provided by Bayer, was consistent with a causal association. Thus, even assuming Dr. Langer had a reliable method for rejecting Valenzuela 2017 entirely (which he does not), he was *still* obliged to apply the Bradford Hill factors in a rigorous fashion, which he did not do.

For example, Dr. Langer's analysis of "plausibility" is a single erroneous sentence, p. 42, that ignores the mountains of evidence compiled by Plaintiffs' experts and instead deems a causal relationship implausible because of a lack of data showing an increased risk of intracranial hypertension in women using oral contraceptives. This minimal analysis is already inadmissible as insufficiently reliable, but, even worse, his analysis of IH in woman using oral contraceptives is itself wholly unreliable, as described *infra*.

Through a variety of conjectural opinions that Dr. Langer never explained in his report, opinions that Dr. Langer admits he has no data to support and which Dr. Langer cannot reduce to

any degree of calculation or quantification, Dr. Langer concluded that he would not suspect any association between IH and Mirena until he "[saw] a rate something considerably above 22 per 100,000 in Mirena users in order to have an increased level of suspicion." *Deposition of Dr. Langer*, 42:14-43:6. Thus, before even *beginning* a causal assessment, Dr. Langer would demand proof that Mirena users were experiencing IH at "a rate something considerably above" the rate of IH in obese women of childbearing women, which is the highest rate of IH in any population on Earth.

The basis of this absurd threshold is Dr. Langer's own unreliable, unquantifiable, and impossible to objectively review conclusion that Mirena users are far more likely to be obese than the population—a conclusion he reached despite conceding he did not have sufficient data to make any reliable estimate of the rate of obesity among Mirena users. *Deposition of Dr. Langer*, 39:22-42:1. Below is just one example of the many times Dr. Langer admitted he did not have any data to support conclusions essential to his opinion, such as the prevalence of obesity among Mirena users:

> Q. Okay. And number 2 says, "The percentage of Mirena users who have a BMI greater than or equal to 30 is blank in the United States and blank in Denmark."
> A. **I don't think we have any data to bear on that.** We know from a number of studies that there's a strong precedence for Mirena among heavier women. But I'm not aware of anything other than, you know, individual clinic reports, and **have no idea** of the source of national data.
> Q. So as with all of your work researching this case and understanding this issue, is it your answer that you are unable to quantify at all the percentage of Mirena users who have a BMI greater than or equal to 30 in the United States?
> A. I'm a scientist, so for approximations when there's a specific BMI greater than 30, I would like to see distributions of data that allow me to address that. And other than looking at individual clinics, like in St. Louis, like in Honolulu, like in Philadelphia, I am not aware of any national data for the United States and I'm not aware of any national data for Denmark.

Deposition of Dr. Langer, 27:16-28:13. Dr. Langer's opinions have no reliable scientific basis and should be precluded in their entirety.

IV. Dr. Langer Admittedly Applied Subjective Methods When Assessing Literature, Adjusting His Analysis To Suit His Conclusions

An expert must "employ[ ] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *Kumho Tire Co.* at 156. Dr. Langer did not. As one example, Dr. Langer admitted that his use of statistical significance in evaluating literature was entirely subjective and selective, and that he freely disregarded it when it suited his purposes:

> Q. Let me put it aside then and just ask you, have you ever seen any paper anywhere that showed with statistical significance that there was no association with pseudotumor cerebri and oral contraceptives?
> MR. GOOLD: Objection.
> THE WITNESS: I think you're misunderstanding the way that statistical significance is used. The lack of statistical significance essentially then endorses the null hypothesis so that there is not evidence for an association. Typically, the way that studies are designed, you would have statistical significance if there was an association, not in the absence of an association.
> BY MR. KENNERLY:
> Q. So you said the lack of statistical significance endorses the null hypothesis. Why did you not conclude the same when you reviewed Mosher 2017 that found that obese class women are not statistically significantly more likely to use IUDs?
> A. As I said when we talked about Mosher, that's one paper in a mix of multiple papers that does not have a statistically significant result for that particular category. Putting it in the context of all of the available evidence, it's not inconsistent with the other papers that do show a relationship. The point estimate is still elevated. It's just not statistically significant.

Deposition of Dr. Langer, 141:3-142:8.

In other words, Dr. Langer *accepted* the null hypothesis and concluded contraceptive users were not more likely to develop IH due to modest increases that lacked statistical significance, but *rejected* the null hypothesis and concluded obese women were more likely to use Mirena due to modest increases that lacked statistical significance. Such a "method," in which a modest increase in an event that lacked statistical significance can both prove and disprove the null hypothesis, is no method at all.

A. Dr. Langer Rejected Half Of Etminan 2015, Relied Upon Half Of Etminan 2015, Then Abandoned The Latter At Deposition But Without Reconsidering His Overall Opinions

As discussed generally in the Omnibus Brief, § IV(A), Dr. Langer recounts the multiple failings of Etminan 2015 as a basis for rejecting the first half of the study showing an increased risk of IH among Mirena users, but then inexplicably relies upon the second half of the study without even attempting to address the admitted limitations of it, much less the criticisms raised by Dr. Friedman's letter to the editor. As Dr. Langer wrote:

> Errors were again made in the study design, but despite its limitations, this analysis-which is, to my knowledge, the only published analysis of IIH risk delineated by progestin type-found no difference in IIH risk for users of Mirena versus users of oral contraceptives containing progestins other than LNG. As multiple studies have evaluated IIH in users of oral contraceptives and found no association, these findings argue against a causal relationship.

Report of Dr. Langer, p. 24. This analysis, which makes no effort to address the significant "errors" and "limitations," is neither objective nor scientific; it is simply accepting evidence Dr. Langer believes will support his argument. At deposition, after thorough questioning, Dr. Langer finally abandoned it entirely:

> Q. Dr. Langer, do you believe the Etminan 2015 paper is a reliable basis to conclude that there is no difference in the risk of IIH for users of Mirena versus users of oral contraceptives containing progestins other than LNG?
> A. I don't believe it's a reliable study.
> Q. So it's not a reliable basis to conclude there is no difference in the risk of IIH for users of Mirena versus users of oral contraceptives containing progestins other than ING?
> A. Yes, that's correct.

124:5-124:15. Yet, as detailed by his report, this same admittedly unreliable analysis was part and parcel of his conclusions about whether or not Mirena is capable of causing or contributing to IH. These opinions should be precluded, along with all opinions based upon it, such as Dr. Langer's conclusions about "a causal relationship" between Mirena and IH.

B. Dr. Langer Disregarded The Norplant Literature Based Upon Conjecture About Preferential Prescribing

As discussed generally in the Omnibus Brief, § IV(B), Dr. Langer's analysis of the Norplant literature and data is subjective and unscientific. Dr. Langer makes no mention of literature concluding, *inter alia*, "there is a well established relationship between PTC and levonorgestrel-releasing implants. Headache is a common adverse effect of levonorgestrel; patients developing headaches or visual disturbances while using it should be evaluated for funduscopic evidence of PTC."[4]

Instead, Dr. Langer raises "possible confounders," such as obesity, and then concludes—through a subjective analysis that is impossible to review or challenge in any objective fashion—the potential for cofounding permits him to conclude he is "not aware of any reliable evidence showing that Norplant causes IIH." *Report of Dr. Langer*, p. 22. Having summarily dismissed the Norplant evidence through conjecture about the possibility of confounding (an analysis that is also unreliable, as discussed *infra*), Dr. Langer does not use it in his causal assessment. Dr. Langer's dismissive review, in contrast to a proper weighing of the evidence, is simply not sufficient to overcome *Daubert*.

C. Dr. Langer's Analysis Of Oral Contraceptives And IH Was Not Scientific

As described generally in the Omnibus brief, Dr. Langer supported his opinions about Mirena and IH with conclusions about the lack of an association between "oral contraceptives" and IH, a conclusion supported by five studies: Digre 1984, Durcan 1988, Ireland 1990, Giuseffi 1991, Radhakrishnan 1993, all of which were either small studies with 1:1 or 1:2 case:control ratios or were "postcard surveys" of doctors in particular regions. Dr. Langer failed to address

[4] Friedman DI. Medication-induced intracranial hypertension in dermatology. Am J Clin Dermatol 2005;6:29–37. This article remains a standard text in the field, and it is cited by several of the studies Defendants' experts rely on, such as Daniels 2007.

the three independent problems identified by the Omnibus brief: all five studies addressed "oral contraceptives" in general, without any regard to levonorgestrel; he never explained how he can use aggregated "oral contraceptives" to draw conclusions about oral contraceptives containing levonorgestrel, nor did he address how those same contraceptives that included levonorgestrel *also* included synthetic forms of estrogen, such as ethinyl estradiol; and, although Dr. Langer cited potential confounding by obesity as his reason for rejecting the Norplant and Mirena literature, he made no effort to address how *none* of those studies controlled for confounding *at all*, much less on a patient-by-patient basis.

At deposition, Dr. Langer claimed he had a new poster abstract to support his opinions on oral contraceptives and IH, Kilgore 2017. This opinion similarly did not survive even the most basic scientific examination, because the study, a small case-control study, had an extraordinary p-value, .415, which Dr. Langer agreed was "slightly less likely to be the result of chance than a coin flip," but which he said he could still use because "this study looked for an association and it did not find one. So it's consistent with the other studies," an unscientific method better described as confirmation bias. Deposition of Dr. Langer 149:15-150:8.

As discussed in the Omnibus brief, none of Bayer's experts have reliably evaluated the literature and data relating to oral contraceptives to IH, and their opinions should be precluded.

V. Dr. Langer Draws Broad Conclusions From Limited Data Without Explanation And Without Addressing Contrary Data, Then Relies On Those Unsupportable Conclusions For His Overall Opinions

The bulk of Dr. Langer's report is devoted to justifying three ways to avoid weighing the literature and data showing a causal association between Mirena and IH: asserting "preferential prescribing" to obese women irredeemably confounds all case reports and case-control studies; "correcting" Valenzuela 2017 by radically raising the number of controls in the Mirena group while radically lowering the number of controls in the non-Mirena group; and, using the

supposed *lack* of disproportionate adverse event reporting as evidence against a causal association. None of these conclusions withstand the scrutiny required by *Daubert*.

A. Dr. Langer Does Not Have A Reliable Method For Concluding "Preferential Prescribing" Exists, Is Unable To Quantify Its Extent, And Did Not Perform The Basic Analyses That Would Show If Preferential Prescribing Or Confounding By Indication Make Any Difference

First, the studies cited by Dr. Langer are not sufficient to conclude, with any degree of reliability, that Mirena is "preferentially prescribed" to obese women. None of the studies cited—Peipert 2011, Scott-Ram 2012, Saito-Tom 2015, Bhuva 2017, and Mosher 2017—concluded as much, and none even *addressed* the extent to which Mirena was prescribed to *anyone*. At Dr. Langer's deposition, these limitations of these studies became almost comical, as he ran away from the very sources he used to support his opinion:

> Q. Okay. And number 2, the study encouraged Levonorgestrel IUD use, and the authors recognized that women came to the study for LNG IUD and the providers were biased towards it. That is in the second column there as the quote from Piepert where they describe that. Do you agree with that?
> A. **Well, it was a study of LARCs, not necessarily Mirena**. But -- so the second column.
> …
> Q. Now**, do you agree with me that the authors themselves recognized that women may have been disproportionally coming to the study to obtain Levonorgestrel IUDs and that there might be a provider bias in favor of it?**
> **A. They cite that as one of a whole series of reasons for why the Mirena IUD was preferentially selected.**

Deposition of Dr. Langer, 102:7-104:4. Dr. Langer's uncritical use of these studies to draw sweeping conclusions about "preferential prescribing," without addressing the studies' limitations nor explaining his method, is unreliable and should be precluded.

Dr. Langer further admitted he made no effort to analyze the extent of "preferential prescribing" beyond "just looking at the numbers as somebody who does a lot of statistics:"

> Q. Now, if you were going to rely on this to say, as you did, that Mirena users are more frequently overweight and obese than users of other contraceptive methods, then should you not have calculated a statistical test to see if this was statistically

significant?

A. This is one of several sources that I looked at to support that statement. Again, on the face this table suggests that Mirena is preferred by overweight and obese women.

Q. And you can conclude this without performing any statistical analysis, correct?

A. This is one of a number of sources that I relied on to make that statement. **And no, I did not perform a statistical test for this**. But looking at the numbers, it would be likely that if you were to stratify by normal and underweight on the one side, and normal weight and obese on the other side, you would find a statistical significant difference**. I did not do that test, but just looking at the numbers as somebody who does a lot of statistics, it would seem to segment out that way.** And there aren't nearly as great differences for any of the other contraceptives in the table.

Q. Is there a reliable epidemiological method to just look at the numbers as somebody who does a lot of statistics?

A. As I said, this is one of several forms of or several studies that I relied on to come to that opinion. And this supports it. It is not -- again, not a statistical test of that particular difference, **but it would appear to be so**.

Deposition of Dr. Langer 106:23-108:24. It is difficult to imagine a more unreliable and subjective method than to "just look at the numbers" in a handful of limited studies, speculate about what they "seem" or "appear" to represent, and then draw sweeping conclusions about whole populations.

Eventually, Dr. Langer admitted that his "method" was to assume there was preferential prescribing and then to conclude it had to be true because it had not been proven not to be true:

Q. And you're comfortable reaching these conclusions even though one of the studies did not reach statistical significance, correct?

A. Again, we take the totality of the evidence, and the paper that you're citing that did not have statistical significance did have a point estimate that showed an increased preference; it was just not statistically significant. As we talked about earlier, not everything has to meet the test of statistical significance. We were talking about a P-value. A P-value of .05 or .06 sometimes would be meaningful? Yes, it can. We take the totality of evidence and look for consistencies within it. **I've seen absolutely nothing published that shows there is not a preference for Mirena among obese, overweight and morbidly obese women**. All of the published information, some of it not statistically significant, but some of it plainly showing trends, demonstrates that there is a preference, and nothing shows that it goes the other way.

Deposition of Dr. Langer, 132:22-134:8 (emphasis added). Such a "method" is not scientific and should be precluded, along with all opinions of Dr. Langer that rely on these conclusions, including his opinions about general causation.[5]

Second, *even if* "preferential prescribing" were a genuine phenomenon, Dr. Langer has not *applied* that supposed fact in any reliable manner to conclude that "confounding by indication" could impact the existing literature and data. Dr. Langer notes that the incidence of IH among obese women is 22/100,000, compared to 6.8/100,000 among all women. But Dr. Langer never addresses how the vast majority of obese women (99,978/100,000) do *not* develop IH, and so "preferential prescribing" would have a minimal impact on studies.

The odds of an obese woman developing IH in any given year (1-in-4,545) are modestly *lower* than the odds of being dealt a four-of-a-kind in Poker (1-in-4,164). The risk of IH among any population, including obese women of childbearing age, is so low that "adjusting" for factors like obesity will make little difference to the odds ratio in a case-control study. Although an "adjustment" of this sort would be trivial to do, such as adding another "stratum" to a 2x2 table to reflect the supposed preferential prescribing, but Dr. Langer never attempted to do so, and instead proffered the subjective, conjectural opinion that there is sufficient "confounding by indication," measured in a purely subjective fashion, that he can disregard the literature and data entirely. Such opinions are speculative and impossible to evaluate objectively. *See* Omnibus Brief, § II (B) & (D).

B. Dr. Langer Cannot Justify The "Corrections" He Made To Valenzuela 2017

[5] *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007)("He reaches his opinion by first identifying his conclusion-- causation at 200 mg/d--and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion. Dr. Doherty's opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science;' it is therefore inadmissible.")

In the Utah portion, Dr. Langer arbitrarily moved 17,682 women from the non-Mirena control group to the Mirena control group, thereby substantially lowering the odds ratio. The justification for this "correction"—a blatant numbers-fixing method unsupported by any literature cited by any of Bayer's experts, in which the actual University of Utah Mirena billing data used by Valenzuela was discarded—was an estimate that 10% of women in Utah use Mirena.

The "method" behind this 10% estimate is a convoluted five-step process that mixes together four surveys and an analysis of the same University of Utah billing database that Valenzuela 2017 used and Dr. Langer rejected. The supposed calculation multiplies together the percent of women aged 18-44 in Utah at risk for unintended pregnancy who used a LARC (Boulet 2016), the percent of women nationwide at risk for unintended pregnancy who did not use contraception (Jones 2012), the percent of all women aged 15-44 nationwide who used a LARC (Branum 2015), the percent of women nationwide who used an IUD (Kavanaugh 2015), and the percent of women at the University of Utah aged 15-44 who had Mirena implanted as compared to another IUD (Sanders 2017, Sanders also being a co-author of Valenzuela). This "method" is a classic opinion "so unrealistic and contradictory as to suggest bad faith or to be in essence an apples and oranges comparison,"[6] and it should be precluded on that basis alone.

Unsurprisingly, none of Bayer's experts actually performed the calculation in their report. At deposition, Dr. Langer admitted his report did not contain the full calculation: "It is not stated. But as you know, Jones is on my materials list." *Deposition of Dr. Langer*, 79:17-80:8. Because neither Dr. Langer nor any of Bayer's other experts revealed in their report the use of Jones 2012 for this purpose (instead burying it in reliance materials), and Dr. Langer was the first

[6] *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir.1996).

epidemiologist deposed, counsel at deposition was unprepared to cross-examine him on it.[7] Defendants' science-by-ambush, however, does not survive *Daubert*: Dr. Langer's use of Jones 2012 "to further discount that 14 percent [found by multiplying Boulet 2016's 18.9% by Sanders 2017's 75%] for the fraction of women in Utah who would not be at risk for unintended pregnancy" is simply wrong.

The unknown numbers that Dr. Langer is trying to find are the number of women in Utah at risk, and not at risk, for unintended pregnancy. Boulet 2016 explicitly provided a number for the women at risk for unintended pregnancy in Utah—256,840, the "weighted" number of their survey of 656 women[8]—but Dr. Langer, like all of Bayer's experts, ignored this number in favor of a convoluted calculation that not only mashed together two completely different datasets, but did so improperly. As Dr. Langer testified:

> **So I need to further discount that 14 percent for the fraction of women in Utah who would not be at risk for unintended pregnancy. And that would be women who were pregnant or immediately postpartum, or didn't have an active sex life and so on.**
>
> **And I used an estimate from a similar data set also from the CDC from a paper by Jones that said that nationally, 62 percent of women at risk for -- well, 62 percent of women were using contraception.** And then there was a further 7.7 percent of women who had had unprotected intercourse within three months who were not looking to become pregnant.
>
> And so that took me to a 70 percent factor to further discount that 14 percent. And so multiplying all of that out it comes to 10 percent. The actual number was 9.9 percent.

Deposition of Dr. Langer, 77:22 to 79:16)(bolding added).

Dr. Langer's "method" is to mash together these two datasets, which he calls "similar:"

Boulet 2016 – Survey of 656 Utah Women	Jones 2012 – National Survey Of

[7] Counsel did, however, bring Jones 2012 to the next epidemiologist deposition, that of Dr. Langer, where Dr. Langer was unable to justify it.

[8] It is trivially easy to use this number alongside Census data for women 18-44 in Utah in 2013 and thereby find the *correct* number that Bayer's experts should have used for their "correction." The end result, however, is that Valenzuela 2017 *still* shows a statistically significant increase in the risk, *even by way of Defendants' own unreliable and improper "correction" of the controls.*

18-44 At Risk For Unintended Pregnancy	Contraceptive Use Among All Women 15-44
??? % Women At Risk For Unintended Pregnancy: "not currently pregnant, were sexually active (not abstinent), and, the last time they had sex, had not had a hysterectomy, did not have a same-sex partner, and did not want a pregnancy."	38% Not Using Contraception: 19% No sex ever / last 3 months 9% Pregnant/postpartum/seeking 10% All Other Reasons
??? % Women Not At Risk For Having An Unintended Pregnancy	62% Using Contraception: 17% Female Sterilization 17% Pill 10% Condom 18% All Other Contraception

Dr. Langer attempts to find the percent of women 18-44 in Utah *not* at risk for an unintended pregnancy by deeming that group from Boulet 2016 to be the same as the women in Jones 2012 who were using contraception. Dr. Langer's "calculation," which neither he nor any other expert disclosed by Bayer revealed in their report, is almost exactly backwards. As Boulet 2016 found, 87.7% of women at risk for unintended pregnancy *were* using contraception, and thus would be included in the *other* group described by Jones 2012, the women using contraception. Conversely, women currently pregnant, who are abstinent, have a hysterectomy, have a same-sex partner, or who want a pregnancy would be extremely unlikely to use any form of contraception, and so would all be included in the *other* group, the women not using contraception. It is improper enough to attempt to mash together these disparate datasets, but it is simply bad faith to do so the wrong way in order to reach the "estimate" that an expert desires.

Dr. Langer's "method" is a classic opinion "so unrealistic and contradictory as to suggest bad faith or to be in essence an apples and oranges comparison,"[9] and so must be precluded. Dr. Langer failed to justify his use of the "10%" estimate for Mirena use in Utah, much less his

[9] *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir.1996).

"correction" of Valenzuela 2017, much less his rejection of Valenzuela 2017, and he should all be precluded from testifying about these issues. *See* Omnibus Brief, § II (B), (C) & (D).

The similar "correction" Dr. Langer performed on the Denmark portion of Valenzuela 2017 should also be rejected: the *sole* basis for "correcting" the Mirena usage numbers[10] is Lindh 2016, a "pure descriptive assessment" of *relative* contraceptive use that made no effort to reflect *absolute* contraceptive use among the population, and which calculated Mirena use by aggregating prescription data and arbitrarily setting "the mean duration of use" to be four years. Indeed, at deposition Dr. Langer admitted he thought the duration of use was based on actual data, rather than an assumption made by the authors:

> Q. So wait a minute. Lindh, you believe, was produced by the Danish Public Authority?
> A. The data came from the Danish Public Authority. Do we have a copy of that here?
> …
> Q. That's data about prescriptions. That's not data about the mean duration of use. In fact, they say right here that they set that to be four years, not that they found that in any data. Correct?
> A. I'm reading this whole section on the methods.
> Q. To your knowledge, you don't know of them finding anywhere other than them saying they set the mean duration there, correct?
> A. Give me a moment here. I'm looking further at the text and the citations. Yes, set that at four years.

Deposition of Dr. Langer, 224:21-226:7. Dr. Langer's method was plainly unscientific, and his use of Lindh 2016 inherently unreliable.

C. Dr. Langer's "Corrected" 2x2 Tables And Odds Ratios Are Unreliable

Dr. Langer's report includes multiple 2x2 tables in which he has "corrected" the figures in Valenzuela 2017 and re-calculated them. The very existence of these re-calculated tables

[10] As with the Utah "correction," the "correction" to the Denmark data by Bayer's experts simply moved 10,021 from the non-Mirena controls to the Mirena controls, thereby significantly lowering the odds ratio. Such is not a reliable method recognized by any literature.

presents a problem of basic logic: if Valenzuela 2017 is unreliable, then how could any "correction" to it be reliable?

At deposition, Dr. Langer provided the unscientific opinion that Valenzuela 2017 was unreliable but his "corrections" are somehow "more reliable," even though he admits they are, at best, an "attempt to try to address what would be supportable" about "how the numbers might come out," an analysis that he would never submit to a peer review journal:

> Q. And this table you did on page 30, which is on Exhibit 5, is that reliable enough that you feel you could submit it to a publication for peer review?
> A. I would have no reason to do that.
> Q. My question is, is it reliable enough that you would submit it to a journal for publication and peer review?
> A. I don't understand the basis of the question. There would never be any reason for me to want to submit something like this for peer review.

Deposition of Dr. Langer, 62:4-63:1, 64:25-65:9, 66:24-67:15 (objections omitted). Eventually, Dr. Langer conceded, "By definition, I started with flawed and incomplete information. However, the flaws in my analysis, which I will grant because I'm using what I agree is flawed information." *Id.* 120:17-120:20. *Daubert* does not permit an expert to use an admittedly flawed analysis.

D. Dr. Langer's Own Analysis Produces "Control" Groups With Rates Of IH Higher Than Any Population Ever Studied

When Dr. Langer, like Bayer's other experts, arbitrarily moved women from the non-Mirena controls to the Mirena controls—a technique unsupported by any literature—the gross impropriety of this "method" produced results demonstrating its unreliability.

A *control*, of course, should be representative of the population in a given study. The rate of IH among women of childbearing age (the population that uses Mirena) is 6.8/100,000. The highest known rate of IH in any population is that in obese women of childbearing years, 22/100,000. Yet, with Dr. Langer's adjustments, his "control" groups have outrageously high

rates of IH, and it is only with these unrealistic "controls" that Dr. Langer (and Bayer's other experts) can manufacture the absence of an increased risk. To wit:

<table>
<tr><td>Dr. Langer Report, p. 30</td><td>Dr. Langer Report, p. 33</td></tr>
<tr><td>
<table>
<tr><th></th><th>PTC Yes</th><th>PTC No</th><th>Odds Ratio (OR) = Rate In Exposed / Rate in Unexposed</th></tr>
<tr><td>LNG-IUS Yes</td><td>8</td><td>22,090</td><td>= 8/22,090</td></tr>
<tr><td>LNG-IUS No</td><td>51</td><td>198,814</td><td>= 51/198,814</td></tr>
</table>
Dr. Langer's "LNG-IUS Yes" group has Mirena exposure at Dr. Langer's assumed rate of women in Utah (10%).

Dr. Langer's "LNG-IUS No" group has PTC at a rate of 51/198,814, or 25.65 per 100,000, far above the rate of PTC among women of childbearing age in Utah.
</td><td>
<table>
<tr><th></th><th>PTC Yes</th><th>PTC No</th><th>Odds Ratio (OR) = Rate In Exposed / Rate in Unexposed</th></tr>
<tr><td>LNG-IUS Yes</td><td>8</td><td>15,488</td><td>= 8/15,488</td></tr>
<tr><td>LNG-IUS No</td><td>56</td><td>139,389</td><td>= 56/139,389</td></tr>
</table>
Dr. Langer's "LNG-IUS Yes" group has Mirena exposure at Dr. Langer's assumed rate of women in Denmark (10%).

Dr. Langer's "LNG-IUS No" group has PTC at a rate of 56/139,389 or 40.18 per 100,000, far above the rate of PTC among women of childbearing age in Denmark.
</td></tr>
</table>

Thus, Dr. Langer's non-Mirena "control" group has PTC over three times more frequently than "females of childbearing age," the population that uses Mirena, PTC more frequently than do obese women 15–44 years of age, and PTC more frequently than any population ever studied.

At deposition, Dr. Langer was shown this exact same chart, and these same conclusions (Deposition Exhibit #22), and given a chance to explain it. Dr. Langer was unable to explain why his "controls" bear no relationship to women in general, Mirena patients, or even obese women of childbearing age:

> Q. All right. And that group of women who don't have Mirena has a rate of pseudotumor of 25.65 per 100,000 in the Utah group in your adjusted analysis, correct?
> A. Correct, yes.
> Q. Does that sound appropriate as a comparison group to create this group of women who don't use Mirena who somehow have pseudotumor among them more commonly than obese women of childbearing age?
> THE WITNESS: Well, if we go on Kilgore, this is quite comparable to obese

> women of childbearing age with pseudotumor. And the case -- or, you know, the numerator is coming straight from the Valenzuela data.
> BY MR. KENNERLY:
> Q. Yes, but the denominator is coming from you changing the numbers. So in your own analysis here, it is your opinion that 100 percent of the 198,814 women who visited the University of Utah did not have Mirena, 100 percent of them were obese?
> A. Where do you get that from the numbers that I put here?
> Q. Why is the rate of pseudotumor so high among women without a Mirena in your adjusted analysis?
> A. I can't speak for that. I can only -- again, this is attempting to correct a study rife with methodologic errors. And the primary correction that I'm making here has to do with the gross underestimate that is not supportable on its face for Mirena exposure. I'm not making any assumptions here about obesity in the control group.

Deposition of Dr. Langer, 222:10-224:4.

Dr. Langer thus "can't speak for" why his "control" group is not representative of any population, much less women in Utah (which was the sole basis for his "corrections"), and he admittedly did not consider, much less analyze with a reliable scientific method, the effect his "correction" had on the control group. Such is, again, a classic opinion "so unrealistic and contradictory as to suggest bad faith or to be in essence an apples and oranges comparison,"[11] and it should be precluded.

E. Dr. Langer Admitted That His Preferred Method For Conducting A Case-Control Study (In Contrast To Valenzuela) Would Not Have Produced A Meaningful Result

Dr. Langer opined that Valenzuela 2017 should have been done a completely different way, by matching each of the 59 IH patients to two controls. Yet, he admitted that he had never rigorously analyzed this issue, and that his hypothetical study would not be sufficiently powered to produce the result he demands, i.e., a statistically significant increase in the risk:

> Q. Now, with a disease as rare as pseudotumor cerebri, is there any situation, any distribution of cases and controls in which that comparison would produce a result with a P-value below .05?
> THE WITNESS: There could be, but given what I understand about the

[11] *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir.1996).

> relationship, it would be highly unlikely, almost certainly that study would show a P-value considerably much greater than .05.

Deposition of Dr. Langer, 76:3 to 77:3. Dr. Langer does not need to identify a superior study design to Valenzuela, but the fact that his own preferred design would *not* produce the result he demanded of Valenzuela is evidence of the subjective and unreliable nature of his "method."

F. Dr. Langer Improperly Attempts To "Have It Both Ways" With Adverse Event Disproportionality, And Conceded The Data From The Empirica Analysis Bayer Withheld From Him Is Supportive Of A Causal Association

Like most of Bayers' experts, Dr. Langer conceded the difficulty of relying upon adverse event data in assessing a causal association. *Report of Dr. Langer*, p. 8. Inexplicably, he also used those same adverse event disproportionality studies as not "support[ing] a relationship between Mirena and IIH." *Id.* at 24.[12] There are three problems with these analyses.

First, it is difficult to imagine a *less* reliable method than one in which an expert admits upfront that certain data should not be used a certain way and then proceeds to use that data in that way. Either adverse event disproportionality studies can be used in causal assessments or they cannot; there is no logical, much less reliable and scientific, way to do both. *See* § II (C).

Second, Dr. Langer's opinion is cursory, subjective, and made without reference to any literature supporting their methods, such as by absurdly comparing the *rate at which adverse events are reported* to the *rate of the disease in the population*, a method explicitly rejected by the FDA, which emphasizes that adverse event reporting can never be directly compared to the population as a whole given that the extent of underreporting is unknown, as is the denominator.[13]

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[12] See also p. 37 (relying on "reporting frequency" of adverse event reports as evidence not supporting causal association) and p. 40 (asserting "disproportional reporting" is relevant to "evidence [of] a true association between Mirena and IIH") and p. 41 (adverse event "reporting rate" is evidence "that there is no meaningful association").

[13] FDA Guidance For Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic

Third, Dr. Langer was not provided with Bayer's own internal disproportionality analyses. At Bayer, the threshold for disproportionate adverse event reporting is to have more than 3 cases, a proportional reporting ratio (PRR) of 2 of more, and a Chi^2 of 4 or more. As of August 1, 2014, which is as far back as Defendants provided the Empirica data, Bayer's own signal detection database showed for IH and Mirena 41 cases, a PRR of 3.883, and Chi^2 of 52.995. As of December 1, 2017, the cases were 440, the PRR was 44.456, and the Chi^2 was 3,224.846. At deposition, Dr. Langer admitted a PRR greater than 40 would "certainly" support causation, that he "[has] never seen a Chi^2" greater than 3,000, and that it "would be consistent with a causal association." *Deposition of Dr. Langer*, 188:2-189:22.

It is no mystery why Bayer did not provide the Empirica data to their experts: it directly contradicts their opinions. That failure renders their opinions on disproportionality, and the causation opinions the experts made in reliance on them, inadmissible. *See* § II (C).

VI. Conclusion

Dr. Langer's opinions suffer numerous fatal flaws in addition to the myriad of issues that his opinions share with Bayer's other disclosed experts, as identified in Plaintiffs' Omnibus Brief. Most egregiously, in the face of evidence withheld from Dr. Langer by the very party that retained him, Dr. Langer was forced to concede that the numbers are actually supportive of a causal association, as Plaintiffs' experts contend.

Dr. Langer's opinions are unreliable and were produced by an unreliable method without reviewing the admittedly relevant data. His testimony should be excluded.

Respectfully submitted,

/s/ Maxwell S. Kennerly

Assessment, p. 11: "for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate."

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing was filed via the ECF/CM system with the Clerk of the Court, which will have sent notice to all attorneys of record in this matter on March 2, 2018.

/s/ *Maxwell S. Kennerly*
Maxwell S. Kennerly